Docket No.:PB-0011-1 DIV

Response Under 37 C.F.R. 1.116 - Expedited Procedure
Examining Group

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By: _____ Printed: Jeannie G. Labra

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of: Kaser et al.

Title:	POLYCYCLIC AROMATIC HYDROCARBON INDUCED MOLECULES		
Serial No.:	09/838,044	Filing Date:	April 18, 2001
Examiner:	Liu, S	Group Art Unit:	1653

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BRIEF ON APPEAL

Sir:

Further to the Notice of Appeal filed September 25, 2003, and received by the USPTO on September 29, 2003, herewith are three copies of Appellants' Brief on Appeal. Appellants hereby request a one-month extension of time in order to file this Brief. Authorized fees include the statutory fee of $110.00 for a one-month extension of time, as well as the $ **330.00** fee for the filing of this Brief.

This is an appeal from the decision of the Examiner finally rejecting claims 15, 16 and 19 of the above-identified application.

(1) REAL PARTY IN INTEREST

The above-identified application is assigned of record to Incyte Pharmaceuticals, Inc. (now Incyte Corporation, formerly known as Incyte Genomics, Inc.) (Reel 010656, Frame 0493), which is the real party in interest herein.

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(2) RELATED APPEALS AND INTERFERENCES

Appellants, their legal representative and the assignee are not aware of any related appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the instant appeal.

(3) STATUS OF THE CLAIMS

Claims rejected:	Claims 15, 16 and 19.
Claims allowed:	(none).
Claims canceled:	Claims 26-39.
Claims withdrawn:	1-14, 17, 18, and 20-25.
Claims on Appeal:	Claims 15, 16 and 19 (A copy of the claims on appeal, as amended, can be found in the attached Appendix).

(4) STATUS OF AMENDMENTS AFTER FINAL

There were no amendments submitted after Final Rejection.

(5) SUMMARY OF THE INVENTION

Appellants' invention is directed to a polypeptide, SEQ ID NO:6, comprising the product of a gene that is expressed in response to polycyclic hydrocarbons (PAH). The invention further comprises an immunogenic fragment of said protein for making antibodies to the protein, and a composition comprising the protein and a suitable pharmaceutical carrier. See specification, at page 4. PAH, such as benzo(a)pyrene (BP) are described in the specification, and the art of record, as ubiquitous environmental pollutants known to cause cancer in laboratory animals, i.e., are carcinogenic. Human exposure to PAH is also shown to be associated a higher incidence of certain cancers. See specification, at page 1. It is further disclosed in the specification, and the art of record, that there is growing evidence that predisposition to cancer may reside in polymorphic genes involved in carcinogen metabolism and repair. One major goal of epidemiologists is to identify individuals who are exposed to high levels of carcinogen, carry cancer-predisposing genes, and lack protective genes. See specification, at page 2. Therefore, the identification of genes and their encoded proteins such as the instant SEQ ID NO:6, that are

induced by exposure to carcinogens such as BP, provides potential diagnostic agents as well as potential therapeutic targets for cancer, or a predisposition for cancer, arising from PAH exposure. See specification, bottom of page 2.

(6) ISSUES

1. Whether claims 15, 16 and 19 directed to polypeptide sequences encoded by genes expressed in response to PAH meet the utility requirement of 35 U.S.C. §101.

2. Whether one of ordinary skill in the art would know how to use the claimed sequences, e.g., in toxicology testing, drug development, and the diagnosis of disease, so as to satisfy the enablement requirement of 35 U.S.C. §112, first paragraph.

3. Whether an immunogenic fragment of SEQ ID NO:6, or a composition comprising the polypeptide of SEQ ID NO:6 or an immunogenic fragment of SEQ ID NO:6, are sufficiently described in the specification that one skilled in the art would recognize applicants possession of them in accordance with 35 U.S.C. §112, first paragraph.

4.

(7) GROUPING OF THE CLAIMS

As to Issue 1

All of the claims on appeal are grouped together.

As to Issue 2

All of the claims on appeal are grouped together.

As to Issue 3

All of the claims on appeal are grouped together

(8) APPELLANTS' ARGUMENTS

Claims 15, 16 and 19 stand rejected under 35 U.S.C. §§ 101 and 112, first paragraph, based on the allegation that the claimed invention lacks patentable utility. The rejection alleges

in particular that:

- the claimed invention is not supported by either a well established or disclosed specific and substantial credible utility. The claimed protein is not supported by a specific asserted utlility because the disclosed use of the protein is generally applicable to screen a library of molecules, to purify a ligand from a sample, and thus is not a particular of the pharmaceutical composition set forth in claim 19. The specification sets forth use of the claimed protein (e.g., SEQ ID NO:6 polypeptide) for treating a disease state associated with altered expression of a gene in response to polycyclic aromatic hydrocarbon (PAH) exposure. However, there is no working examples and guidance and no support as to how to make and use it in the specification regarding the claimed protein; the specification only provides evidence for human tissue expression at the polynucleotide level NOT biologically active protein level. Thus, there is no specific utility associated with the protein.

The rejection of claims 15, 16 and 19 is improper, as the inventions of those claims have a patentable utility as set forth in the instant specification, and/or a utility well-known to one of ordinary skill in the art.

The invention at issue is identified in the patent application as a polypeptide sequence encoded by a polynucleotide that is expressed in human liver tissue in response to PAH treatment. As such, the claimed invention has numerous practical, beneficial uses in toxicology testing, drug development, and the diagnosis of disease, none of which require knowledge of how the polypeptide actually functions.

There is, in addition, direct proof of the utility of the claimed invention. Applicants previously submitted the Declaration of Lars Michael Furness in the response filed May 16, 2003 describing some of the practical uses of the claimed invention in gene and protein expression monitoring applications as they would have been understood at the time of the patent application. The Furness Declaration describes, in particular, how the claimed polypeptide can be used in protein expression analysis techniques such as 2-D PAGE gels and western blots. Using the claimed invention with these techniques, persons of ordinary skill in the art can better assess, for example, the potential toxic effect of a drug candidate. (Furness Declaration at ¶ 10).

The Patent Examiner does not dispute that the claimed polypeptide can be used in 2-D PAGE gels and western blots to perform drug toxicity testing. Instead, the Patent Examiner contends that the claimed polypeptide cannot be useful without precise knowledge of its function. But the law never has required knowledge of biological function to prove utility. It is the claimed invention's uses, not its functions, that are the subject of a proper analysis under the utility requirement.

Applicants further submit three additional expert Declarations under 37 C.F.R. § 1.132, with respective attachments, and seven (7) scientific references. The Furness Declaration, Rockett Declaration, Bedilion Declaration, Iyer Declaration, and the seven (7) references fully establish that, prior to the August 30, 1999 filing date of the parent Kaser '493 application, it was well-established in the art that:

> expression analysis is useful, *inter alia*, in drug discovery and lead optimization efforts; in toxicology, particularly toxicology studies conducted early in drug development efforts; and in phenotypic characterization and categorization of cell types, including neoplastic cell types;
>
> expression analysis can be performed by measuring expression of either proteins or of their encoding transcripts;
>
> it is not necessary that the biological function of a gene be known for measurement of its expression to be useful in drug discovery and lead optimization analyses, toxicology, or molecular phenotyping experiments;
>
> antibodies can routinely be prepared that specifically identify the protein immunogen; used as gene expression probes, such antibodies generate a signal that is specific to the protein, that is, produce a gene-specific expression signal;
>
> each additional gene-specific probe used as a tool in expression analysis provides an additional gene-specific signal that could not otherwise have been detected, giving a more comprehensive, robust, higher resolution, statistically more significant, and thus more useful expression pattern in such analyses than would otherwise have been possible;
>
> biologists, such as toxicologists, recognize the increased utility of more comprehensive, robust, higher resolution, statistically more significant results, and thus want each newly identified expressed gene to be included in such an analysis;
>
> failure of a probe to detect changes in expression of its cognate gene (because such changes did not occur in a particular experiment) does not diminish the

usefulness of the probe as a research tool, because such information is itself useful; and

failure of a probe completely to detect its cognate transcript in any particular expression analysis experiment (because the protein is not normally expressed in that sample) does not deprive the probe of usefulness to the community of users who would use it as a research tool.

Applicants file herewith:

1. the Declaration of John C. Rockett, Ph.D., under 37 C.F.R. § 1.132, with Exhibits A-Q (hereinafter the "Rockett Declaration");

2. the Declaration of Tod Bedilion, Ph.D., under 37 C.F.R. § 1.132 (hereinafter the "Bedilion Declaration");

3. the Declaration of Vishwanath R. Iyer, Ph.D., under 37 C.F.R. § 1.132 with Exhibits A-E (hereinafter the "Iyer Declaration"); and

4. seven (7) references published before the August 30, 1999 priority date of the instant divisional application:

   a) PCT application WO 95/21944, SmithKline Beecham Corporation, Differentially expressed genes in healthy and diseased subjects (August 17, 1995)

   b) PCT application WO 95/20681, Incyte Pharmaceuticals, Inc., Comparative gene transcript analysis (August 3, 1995)

   c) M. Schena et al., Quantitative monitoring of gene expression patterns with a complementary DNA microarray, Science 270:467-470 (October 20, 1995)

   d) PCT application WO 95/35505, Stanford University, Method and apparatus for fabricating microarrays of biological samples (December 28, 1995)

   e) U.S. Pat. No. 5,569,588, M. Ashby et al., Methods for drug screening (October 29, 1996)

   f) R. A. Heller al., Discovery and analysis of inflammatory disease-related genes using cDNA microarrays, Proc. Natl. Acad. Sci. USA 94:2150 - 2155 (March 1997)

   g) PCT application WO 97/13877, Lynx Therapeutics, Inc., Measurement of gene expression profiles in toxicity determinations (April 17, 1997)

In any event, as demonstrated by the Furness Declaration, the Rockett Declaration, the Bedilion Declaration, the Iyer Declaration, and seven (7) scientific references, the person of ordinary skill in the art can achieve beneficial results from the claimed polypeptide and the claimed methods in the absence of any knowledge as to the precise function of the claimed polypeptide. The uses of the claimed polypeptide and claimed methods for protein expression monitoring applications including toxicology testing are in fact independent of the precise function of the polypeptide.

The Final Office Action is replete with arguments made and positions taken for the first time in a misplaced attempt to justify the rejections of the claims under 35 U.S.C. §§ 101 and 112. This is particularly so with respect to the substantial, specific and credible utilities disclosed in the Kaser '493 application relating to the use of the SEQ ID NO:6 polypeptide for protein expression monitoring applications. Such protein expression monitoring applications are highly useful in drug development and in toxicity testing.

The Examiner's new positions and arguments include that (a) the Kaser '493 application allegedly does not disclose toxicology testing; and (b) the gene expression monitoring results obtained using theSEQ ID NO:6 polypeptide are allegedly "not specific" because the particulars of toxicology testing with the polypeptide SEQ ID NO:6 are not disclosed in the instant specification (Final Office Action, e.g., pp. 8-9). Indeed, the Final Office Action fails to acknowledge, let alone address, the Kaser '493 disclosure that " chip based technologies can be used "for the detection and/or quantification of nucleic acid or protein", and that ""[a] variety of protocols including ELISA, RIA, and FACS for measuring PSEQ are known in the art and provide a basis for diagnosing altered or abnormal levels of expression" (Kaser '493 application at page12.)

Under the circumstances, Appellants are submitting with this Appeal Brief (in triplicate) the Declarations under 37 CFR § 1.132 of Rockett, Bedilion and Iyer, and seven (7) scientific references. As we will show, the Rockett, Bedilion and Iyer Declarations, together with the Furness declaration and seven (7) scientific references shows the many substantial reasons why the Examiner's new positions and arguments with respect to the use of the SEQ ID NO:6 polypeptide in protein expression monitoring applications are without merit.

The fact that the Rockett, Bedilion and Iyer Declarations and seven (7) scientific

references are being submitted in response to positions taken and arguments made for the first time in the Final Office Action constitutes, by itself, "good and sufficient reasons" under 37 C.F.R. § 1.195 why that Declaration was not earlier submitted and should be admitted at this time.

II. The use of the claimed polypeptides for toxicology testing and drug discovery are sufficient utilities under 35 U.S.C. §§ 101 and 112, first paragraph

The claimed invention meets all of the necessary requirements for establishing a credible utility under the Patent Law: There are "well-established" uses for the claimed invention known to persons of ordinary skill in the art, and there are specific practical and beneficial uses for the invention disclosed in the patent application's specification. These uses are explained, in detail, in the Furness Declaration, the Rockett Declaration, the Bedilion Declaration, and the Iyer Declaration. Objective evidence, not considered by the Patent Office, further corroborates the credibility of the asserted utilities.

A. The uses of SEQ ID NO:6 for toxicology testing, drug discovery, and disease diagnosis are practical uses that confer "specific benefits" to the public

The claimed invention has specific, substantial, real-world utility by virtue of its use in toxicology testing, drug development and disease diagnosis through gene expression profiling. These uses are explained in detail in the previously filed Furness Declaration and in the accompanying Rockett Declaration, Bedilion Declaration, and Iyer Declaration, the substance of which is not rebutted by the Patent Examiner. There is no dispute that the claimed invention is in fact a useful tool in two-dimensional polyacrylamide gel electrophoresis ("2-D PAGE") analysis and western blots used to monitor protein expression and assess drug toxicity.

The instant application is a divisional of, and claims priority to, United States patent application Serial No.09/386,493, having the identical Specification, (hereinafter "the Kaser '493 application").

In his Declaration, Mr. Furness explains the many reasons why a person skilled in the art who read the Kaser '493 application on August 30, 1999 would have understood that application to disclose the claimed polypeptide to be useful for a number of gene and protein expression

monitoring applications, *e.g.*, in 2-D PAGE technologies, in connection with the development of drugs and the monitoring of the activity of such drugs. (Furness Declaration at, e.g., ¶¶ 11-15). Much, but not all, of Mr. Furness' explanation concerns the use of the claimed polypeptide in the creation of protein expression maps using 2-D PAGE.

2-D PAGE technologies were developed during the 1980's. Since the early 1990's, 2-D PAGE has been used to create maps showing the differential expression of proteins in different cell types or in similar cell types in response to drugs and potential toxic agents. Each expression pattern reveals the state of a tissue or cell type in its given environment, *e.g.*, in the presence or absence of a drug. By comparing a map of cells treated with a potential drug candidate to a map of cells not treated with the candidate, for example, the potential toxicity of a drug can be assessed. (Furness Declaration at ¶ 11.)

The claimed invention makes 2-D PAGE analysis a more powerful tool for toxicology and drug efficacy testing. A person of ordinary skill in the art can derive more information about the state or states or tissue or cell samples from 2-D PAGE analysis with the claimed invention than without it. As Mr. Furness explains:

> In view of the Kaser '493 application.... and other related pre-August 1999 publications, persons skilled in the art on August 30, 1999 clearly would have understood the Kaser '493 application to disclose the SEQ ID NO:6 polypeptide to be useful in 2-D PAGE analyses for the development of new drugs and monitoring the activities of drugs for such purposes as evaluating their efficacy and toxicity . . . . (Furness Declaration, ¶ 10)
>
> * * *
>
> Persons skilled in the art would appreciate that a 2-D PAGE map that utilized the SEQ ID NO:6 polypeptide sequence would be a more useful tool than a 2-D PAGE map that did not utilize this protein sequence in connection with conducting protein expression monitoring studies on proposed (or actual) drugs for treating cancer for such purposes as evaluating their efficacy and toxicity. (Furness Declaration, ¶ 12)

Mr. Furness' observations are confirmed in the literature published before the filing of the patent application. Wilkins, for example, describes how 2-D gels are used to define proteins present in various tissues and measure their levels of expression, the data from which is in turn used in databases:

For proteome projects, the aim of [computer-aided 2-D PAGE] analysis . . . is to

> catalogue all spots from the 2-D gel in a qualitative and if possible quantitative manner, so as to define the number of proteins present and their levels of expression. Reference gel images, constructed from one or more gels, for the basis of two-dimensional gel databases. (Wilkins, Tab C, p. 26).

In his Declaration, Dr. Rockett explains the many reasons why a person skilled in the art in 1999 would have understood that any expressed polypeptide or expressed polynucleotide is useful for a number of gene and protein expression monitoring applications, *e.g.*, in 2-D PAGE technologies or cDNA microarrays, in connection with the development of drugs and the monitoring of the activity of such drugs. (Rockett Declaration at, e.g., ¶¶ 10-18).

> It is widely understood among molecular and cellular biologists that protein expression levels provide complementary profiles for any given cell and cellular state. [Rockett Declaration, ¶ 11.]

> Thus, as with nucleic acid microarrays, the greater the number of proteins detectable, the greater the power of the technique; the absence or failure of a protein to change in expression levels does not diminish the usefulness of the method; and prior knowledge of the biological function of the protein is not required. As applied to protein expression profiling, these principles have been well understood since at least as early as the 1980s. [Rockett Declaration, ¶ 14.]

> It is my opinion, therefore, based on the state of the art in toxicology at least since the mid-1990s -- and as regards protein profiling, even earlier -- that disclosure of the sequence of a new . . . protein, with or without knowledge of its biological function, would have been sufficient information for a toxicologist to use the . . . protein in expression profiling studies in toxicology.[1] [Rockett Declaration, ¶ 18.]

In his Declaration, Dr. Bedilion explains why a person of skill in the art in 1999 would have understood that any expressed polynucleotide is useful for gene expression monitoring applications using cDNA microarrays. (Bedilion Declaration, e.g., ¶¶ 4-7.) In his Declaration, Dr. Iyer explains why a person of skill in the art in 1999 would have understood that any expressed polynucleotide is useful for gene expression monitoring applications using cDNA microarrays, stating that "[t]o provide maximum versatility as a research tool, the microarray

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[1] "Use of the words 'it is my opinion' to preface what someone of ordinary skill in the art would have known does not transform the factual statements contained in the declaration into opinion testimony." *In re Alton*, 37 USPQ2d 1578, 1583 (Fed. Cir. 1996).

should include – and as a biologist I would want my microarray to include – each newly identified gene as a probe." (Iyer Declaration, ¶ 9.)

B. The use of proteins expressed by humans as tools for toxicology testing, drug discovery, and the diagnosis of disease is now "well-established"

The technologies made possible by expression profiling using polypeptides are now well-established. The technical literature recognizes not only the prevalence of these technologies, but also their unprecedented advantages in drug development, testing and safety assessment. These technologies include toxicology testing, e.g., as described by Furness, Rockett, and Iyer in their Declarations.

Toxicology testing is now standard practice in the pharmaceutical industry. See, *e.g.*, John C. Rockett, et. al., Differential gene expression in drug metabolism and toxicology: practicalities, problems, and potential, Xenobiotica 29:655-691 (July 1999) (of record, filed with the Response to Office Action on May 16, 2003)

> Knowledge of toxin-dependent regulation in target tissues is not solely an academic pursuit as much interest has been generated in the pharmaceutical industry to harness this technology in the early identification of toxic drug candidates, thereby shortening the developmental process and contributing substantially to the safety assessment of new drugs. ((Reference No. 1), page 656)

To the same effect are several other scientific publications, including Emile F. Nuwaysir, et al., Microarrays and Toxicology: The Advent of Toxicogenomics, Molecular Carcinogenesis 24:153-159 (1999); and Sandra Steiner and N. Leigh Anderson, Expression profiling in toxicology -- potentials and limitations, Toxicology Letters 112-13:467-471 (2000) (of record, filed with the Response to Office Action on May 16, 2003).

Nucleic acids useful for measuring the expression of whole classes of genes are routinely incorporated for use in toxicology testing. Nuwaysir et al. describes, for example, a Human ToxChip comprising 2089 human clones, which were selected

> for their well-documented involvement in basic cellular processes as well as their responses to different types of toxic insult. Included on this list are DNA replication and repair genes, apoptosis genes, and genes responsive to PAHs and dioxin-like compounds, peroxisome proliferators, estrogenic compounds, and oxidant stress. Some of the other

> categories of genes include transcription factors, oncogenes, tumor suppressor genes, cyclins, kinases, phosphatases, cell adhesion and motility genes, and homeobox genes. Also included in this group are 84 housekeeping genes, whose hybridization intensity is averaged and used for signal normalization of the other genes on the chip.

See also Table 1 of Nuwaysir et al. (listing additional classes of genes deemed to be of special interest in making a human toxicology microarray). Note, in particular, the reference to genes responsive to PAHs, the subject matter of the instant application.

The more genes – and, accordingly, the polypeptides they encode -- that are available for use in toxicology testing, the more powerful the technique. Control genes are carefully selected for their stability across a large set of array experiments in order to best study the effect of toxicological compounds. See email from the primary investigator of the Nuwaysir paper, Dr. Cynthia Afshari to an Incyte employee, dated July 3, 2000, as well as the original message to which she was responding (of record, filed with the Response to Office Action on May 16, 2003). Thus, there is no expressed gene which is irrelevant to screening for toxicological effects, and all expressed genes have a utility for toxicological screening.

Further evidence of the well-established utility of all expressed polypeptides and polynucleotides in toxicology testing is found in U.S. Pat. No. 5,569,588 (Reference No. 4e) and published PCT applications WO 95/21944 (Reference No. 4a), WO 95/20681 (Reference No. 4b), and WO 97/13877 (Reference No. 4g).

U.S. Pat. No. 5,569,588 ("Methods for Drug Screening") ("the '588 patent"), issued October 29, 1996, with a priority date of August 9, 1995, describes an expression profiling platform, the "genome reporter matrix," which is based upon the measurement of protein expression levels. The '588 patent further describes use of nucleic acid microarrays to measure transcript expression levels, making clear that the utility of comparing multidimensional expression data sets equally applies to protein expression data and transcript expression data.

The '588 patent speaks clearly to the usefulness of such expression analyses, particularly but not exclusively protein expression profiling, in drug development and toxicology, particularly pointing out that a protein's failure to change in expression level is a useful result. Thus, with emphasis added,

> [The invention provides] methods and compositions for modeling the

transcriptional responsiveness of an organism to a candidate drug. . . . [The final step of the method comprises] comparing reporter gene product signals for each cell before and after contacting the cell with the candidate drug to obtain a drug response profile which provides a model of the transcriptional responsiveness of said organism to the candidate drug. [abstract]

The present invention exploits the recent advances in genome science to provide for the rapid screening of large numbers of compounds against a systemic target comprising substantially all targets in a pathway [or] organism. [column 1]

The ensemble of reporting cells comprises as comprehensive a collection of transcription regulatory genetic elements as is conveniently available for the targeted organism so as to most accurately model the systemic transcriptional response. Suitable ensembles generally comprise thousands of individually reporting elements; preferred ensembles are substantially comprehensive, i.e. provide a transcriptional response diversity comparable to that of the target organism. Generally, a substantially comprehensive ensemble requires transcription regulatory genetic elements from at least a majority of the organism's genes, and preferably includes those of all or nearly all of the genes. We term such a substantially comprehensive ensemble a genome reporter matrix. [column 2]

Drugs often have side effects that are in part due to the lack of target specificity. . . . [A] genome reporter matrix reveals the spectrum of other genes in the genome also affected by the compound. In considering two different compounds both of which induce the ERG10 reporter, if one compound affects the expression of 5 other reporters and a second compound affects the expression of 50 other reports, the first compound is, a priori, more likely to have fewer side effects. [columns 2-3]

Furthermore, it is not necessary to know the identity of any of the responding genes. [column 3]

[A]ny new compound that induces the same response profile as [a] . . . dominant tubulin mutant would provide a candidate for a taxol-like pharmaceutical. [column 4]

The genome reporter matrix offers a simple solution to recognizing new specificities in combinatorial libraries. Specifically, pools of new compounds are tested as mixtures across the matrix. If the pool has any new activity not present in the original lead compound, new genes are affected among the reporters. [column 4]

A sufficient number of different recombinant cells are included to provide an ensemble of transcriptional regulatory elements of said organism sufficient to

model the transcriptional responsiveness of said organism to a drug. In a preferred embodiment, the matrix is substantially comprehensive for the selected regulatory elements, e.g. essentially all of the gene promoters of the targeted organism are included. [columns 6-7]

In a preferred embodiment, the basal response profiles are determined. . . . The resultant electrical output signals are stored in a computer memory as genome reporter output signal matrix data structure associating each output signal with the coordinates of the corresponding microtiter plate well and the stimulus or drug. This information is indexed against the matrix to form reference response profiles that are used to determine the response of each reporter to any milieu in which a stimulus may be provided. After establishing a basal response profile for the matrix, each cell is contacted with a candidate drug. The term drug is used loosely to refer to agents which can provoke a specific cellular response. . . . The drug induces a complex response pattern of repression, silence and induction across the matrix . . . .The response profile reflects the cell's transcriptional adjustments to maintain homeostasis in the presence of the drug. . . . After contacting the cells with the candidate drug, the reporter gene product signals from each of said cells is again measured to determine a stimulated response profile. The basal o[r] background response profile is then compared with . . . the stimulated response profile to identify the cellular response profile to the candidate drug. [columns 7-8]

In another embodiment of the invention, a matrix [i.e., array] of hybridization probes corresponding to a predetermined population of genes of the selected organism is used to specifically detect changes in gene transcription which result from exposing the selected organism or cells thereof to a candidate drug. In this embodiment, one or more cells derived from the organism is exposed to the candidate drug in vivo or ex vivo under conditions wherein the drug effects a change in gene transcription in the cell to maintain homeostasis. Thereafter, the gene transcripts, primarily mRNA, of the cell or cells is isolated . . . [and] then contacted with an ordered matrix [array] of hybridization probes, each probe being specific for a different one of the transcripts, under conditions where each of the transcripts hybridizes with a corresponding one of the probes to form hybridization pairs. The ordered matrix of probes provides, in aggregate, complements for an ensemble of genes of the organism sufficient to model the transcriptional responsiveness of the organism to a drug. . . . The matrix-wide signal profile of the drug-stimulated cells is then compared with a matrix-wide signal profile of negative control cells to obtain a specific drug response profile. [column 8]

The invention also provides means for computer-based qualitative analysis of candidate drugs and unknown compounds. A wide variety of reference response profiles may be generated and used in such analyses. [column 8]

Response profiles for an unknown stimulus (e.g. new chemicals, unknown compounds or unknown mixtures) may be analyzed by comparing the new stimulus response profiles with response profiles to known chemical stimuli. [column 9]

The response profile of a new chemical stimulus may also be compared to a known genetic response profile for target gene(s). [column 9]

WO 95/21944 ("Differentially expressed genes in healthy and diseased subjects"), published August 17, 1995, describes the use of nucleic acid microarrays in expression profiling analyses, emphasizing that *patterns* of expression can be used to distinguish healthy tissues from diseased tissues and that *patterns* of expression can additionally be used in drug development and toxicology studies, without knowledge of the biological function of the encoded gene product. In particular, and with emphasis added:

The present invention involves . . . methods for diagnosing diseases . . . characterized by the presence of [differentially expressed] . . . genes, despite the absence of knowledge about the gene or its function. The methods involve the use of a composition suitable for use in hybridization which consists of a solid surface on which is immobilized at pre-defined regions thereon a plurality of defined oligonucleotide/ polynucleotide sequences for hybridization. Each sequence comprises a fragment of an EST. . . . Differences in hybridization patterns produced through use of this composition and the specified methods enable diagnosis of diseases based on differential expression of genes of unknown function. . . . [abstract]

The method [of the present invention] involves producing and comparing hybridization patterns formed between samples of expressed mRNA or cDNA polynucleotide sequences . . . and a defined set of oligonucleotide/polynucleotide[] . . . immobilized on a support. Those defined [immobilized] oligonucleotide/polynucleotide sequences are representative of the total expressed genetic component of the cells, tissues, organs or organism as defined by the collection of partial cDNA sequences (ESTs). [page 2]

The present invention meets the unfilled needs in the art by providing methods for the . . . use of gene fragments and genes, even those of unknown full length sequence and unknown function, which are differentially expressed in a healthy animal and in an animal having a specific disease or infection by use of ESTs derived from DNA libraries of healthy and/or diseased/infected animals. [page 4]

Yet another aspect of the invention is that it provides . . . a means for . . . monitoring the efficacy of disease treatment regimes including . . . toxicological effects thereof. [page 4]

It has been appreciated that one or more differentially identified EST or gene-specific oligonucleotide/polynucleotides define a pattern of differentially expressed genes diagnostic of a predisease, disease or infective state. A knowledge of the specific biological function of the EST is not required only that the EST[] identifies a gene or genes whose altered expression is associated reproducibly with the predisease, disease or infectious state. [page 4]

As used herein, the term 'disease' or 'disease state' refers to any condition which deviates from a normal or standardized healthy state in an organism of the same species in terms of differential expression of the organism's genes. . . [whether] of genetic or environmental origin, for example, an inherited disorder such as certain breast cancers. . . .[or] administration of a drug or exposure of the animal to another agent, e.g., nutrition, which affects gene expression. [page 5]

As used herein, the term 'solid support' refers to any known substrate which is useful for the immobilization of large numbers of oligonucleotide/polynucleotide sequences by any available method . . . [and includes, inter alia,] nitrocellulose, . . . glass, silica. . . . [page 6]

By 'EST' or 'Expressed Sequence Tag' is meant a partial DNA or cDNA sequence of about 150 to 500, more preferably about 300, sequential nucleotides. . . . [page 6]

One or more libraries made from a single tissue type typically provide at least about 3000 different (i.e., unique) ESTs and potentially the full complement of all possible ESTs representing all cDNAs e.g., 50,000 – 100,000 in an animal such as a human. [page 7]

The lengths of the defined oligonucleotide/ polynucleotides may be readily increased or decreased as desired or needed. . . . The length is generally guided by the principle that it should be of sufficient length to insure that it is on[] average only represented once in the population to be examined. [page 7]

Comparing the . . . hybridization patterns permits detection of those defined oligonucleotide/ polynucleotides which are differentially expressed between the healthy control and the disease sample by the presence of differences in the hybridization patterns at pre-defined regions [of the solid support]. [page 13]

It should be appreciated that one does not have to be restricted in using ESTs from a particular tissue from which probe RNA or cDNA is obtained[;] rather any or all ESTs (known or unknown) may be placed on the support. Hybridization will be used [to] form diagnostic patterns or to identify which particular EST is detected. For example, all known ESTs from an organism are used to produce a 'master' solid support to which control sample and disease samples are alternately hybridized. [page 14]

> Diagnosis is accomplished by comparing the two hybridization patterns, wherein substantial differences between the first and second hybridization patterns indicate the presence of the selected disease or infection in the animal being tested. Substantially similar first and second hybridization patterns indicate the absence of disease or infection. This[,] like many of the foregoing embodiments[,] may use known or unknown ESTs derived from many libraries. [page 18]
>
> Still another intriguing use of this method is in the area of monitoring the effects of drugs on gene expression, both in laboratories and during clinical trials with animal[s], especially humans. [page 18]

WO 95/20681 ("Comparative Gene Transcript Analysis"), filed in 1994 by Applicants' assignee and published August 3, 1995, has three issued U.S. counterparts: U.S. Pat. Nos. 5,840,484, issued November 24, 1998; 6,114,114, issued September 5, 2000; and 6,303,297, issued October 16, 2001.

The specification describes the use of transcript expression *patterns,* or "images", each comprising multiple pixels of gene-specific information, for diagnosis, for cellular phenotyping, and in toxicology and drug development efforts. The specification describes a plurality of methods for obtaining the requisite expression data -- one of which is microarray hybridization -- and equates the uses of the expression data from these disparate platforms. In particular, and with emphasis added:

> [The invention provides a] method and system for quantifying the relative abundance of gene transcripts in a biological specimen. . . . [G]ene transcript imaging can be used to detect or diagnose a particular biological state, disease, or condition which is correlated to the relative abundance of gene transcripts in a given cell or population of cells. The invention provides a method for comparing the gene transcript image analysis from two or more different biological specimens in order to distinguish between the two specimens and identify one or more genes which are differentially expressed between the two specimens. [abstract]
>
> [W]e see each individual gene product as a 'pixel' of information, which relates to the expression of that, and only that, gene. We teach herein [] methods whereby the individual 'pixels' of gene expression information can be combined into a single gene transcript 'image,' in which each of the individual genes can be visualized simultaneously and allowing relationships between the gene pixels to be easily visualized and understood. [page 2]
>
> The present invention avoids the drawbacks of the prior art by providing a method to quantify the relative abundance of multiple gene transcripts in a given

biological specimen. . . . The method of the instant invention provides for detailed diagnostic comparisons of cell profiles revealing numerous changes in the expression of individual transcripts. [page 6]

High resolution analysis of gene expression be used directly as a diagnostic profile. . . . [page 7]

The method is particularly powerful when more than 100 and preferably more than 1,000 gene transcripts are analyzed. [page 7]

The invention . . . includes a method of comparing specimens containing gene transcripts. [page 7]

The final data values from the first specimen and the further identified sequence values from the second specimen are processed to generate ratios of transcript sequences, which indicate the differences in the number of gene transcripts between the two specimens. [i.e., the results yield analogous data to microarrays] [page 8]

Also disclosed is a method of producing a gene transcript image analysis by first obtaining a mixture of mRNA, from which cDNA copies are made. [page 8]

In a further embodiment, the relative abundance of the gene transcripts in one cell type or tissue is compared with the relative abundance of gene transcript numbers in a second cell type or tissue in order to identify the differences and similarities. [page 9]

In essence, the invention is a method and system for quantifying the relative abundance of gene transcripts in a biological specimen. The invention provides a method for comparing the gene transcript image from two or more different biological specimens in order to distinguish between the two specimens. . . . [page 9]

[T]wo or more gene transcript images can be compared and used to detect or diagnose a particular biological state, disease, or condition which is correlated to the relative abundance of gene transcripts in a given cell or population of cells. [pages 9-10]

The present invention provides a method to compare the relative abundance of gene transcripts in different biological specimens. . . . This process is denoted herein as gene transcript imaging. The quantitative analysis of the relative abundance for a set of gene transcripts is denoted herein as "gene transcript image analysis" or "gene transcript frequency analysis". The present invention allows one to obtain a profile for gene transcription in any given population of cells or tissue from any type of organism. [page 11]

The invention has significant advantages in the fields of diagnostics, toxicology and pharmacology, to name a few. [page 12]

[G]ene transcript sequence abundances are compared against reference database sequence abundances including normal data sets for diseased and healthy patients. The patient has the disease(s) with which the patient's data set most closely correlates. [page 12]

For example, gene transcript frequency analysis can be used to different normal cells or tissues from diseased cells or tissues. . . . [page 12]

In toxicology, . . . [g]ene transcript imaging provides highly detailed information on the cell and tissue environment, some of which would not be obvious in conventional, less detailed screening methods. The gene transcript image is a more powerful method to predict drug toxicity and efficacy. Similar benefits accrue in the use of this tool in pharmacology. . . . [page 12]

In an alternative embodiment, comparative gene transcript frequency analysis is used to differentiate between cancer cells which respond to anti-cancer agents and those which do not respond. [page 12]

In a further embodiment, comparative gene transcript frequency analysis is used . . . for the selection of better pharmacologic animal models. [page 14]

In a further embodiment, comparative gene transcript frequency analysis is used in a clinical setting to give a highly detailed gene transcript profile of a diseased state or condition. [page 14]

An alternate method of producing a gene transcript image includes the steps of obtaining a mixture of test mRNA and providing a representative array of unique probes whose sequences are complementary to at least some of the test mRNAs. Next, a fixed amount of the test mRNA is added to the arrayed probes. The test mRNA is incubated with the probes for a sufficient time to allow hybrids of the test mRNA and probes to form. The mRNA-probe hybrids are detected and the quantity determined. [page 15]

[T]his research tool provides a way to get new drugs to the public faster and more economically. [page 36]

In this method, the particular physiologic function of the protein transcript need not be determined to qualify the gene transcript as a clinical marker. [page 38]

[T]he gene transcript changes noted in the earlier rat toxicity study are carefully evaluated as clinical markers in the followed patients. Changes in the gene transcript image analyses are evaluated as indicators of toxicity by correlation

> with clinical signs and symptoms and other laboratory results. . . . The . . . analysis highlights any toxicological changes in the treated patients. [page 39]

WO 97/13877 ("Measurement of Gene Expression Profiles in Toxicity Determinations"), filed on October 11, 1996 and published on April 17, 1997 (shortly after the April 8, 1997 filing date of the parent application for the instant U.S. Serial No. 09/203,545 application), describes an expression profiling technology differing somewhat from the use of cDNA microarrays and differing from the genome reporter matrix of the '588 patent; but the use of the data is analogous. As per its title, the WO 97/13877 publication describes use of expression profiling in toxicity determinations. In particular, and with emphasis added:

> [T]he invention relates to a method for detecting and monitoring changes in gene expression patterns in in vitro and in vivo systems for determining the toxicity of drug candidates. [Field of the invention]
>
> An object of the invention is to provide a new approach to toxicity assessment based on an examination of gene expression patterns, or profiles, in in vitro or in vivo test systems. [page 3]
>
> Another object of the invention is to provide a rapid and reliable method for correlating gene expression with short term and long term toxicity in test animals. [page 3]
>
> The invention achieves these and other objects by providing a method for massively parallel signature sequencing of genes expressed in one or more selected tissues of an organism exposed to a test compound. An important feature of the invention is the application of novel . . . methodologies that permit the formation of gene expression profiles for selected tissues . . . . Such profiles may be compared with those from tissues of control organisms at single or multiple time points to identify expression patterns predictive of toxicity. [page 3]
>
> As used herein, the terms "gene expression profile," and "gene expression pattern" which is used equivalently, means a frequency distribution of sequences of portions of cDNA molecules sampled from a population of tag-cDNA conjugates. . .. Preferably, the total number of sequences determined is at least 1000; more preferably, the total number of sequences determined in a gene expression profile is at least ten thousand. [page 7]
>
> The invention provides a method for determining the toxicity of a compound by analyzing changes in the gene expression profiles in selected tissues of test organisms exposed to the compound. . . . . Gene expression profiles derived from test organisms are compared to gene expression profiles derived from control

organisms. . . . [page 7]

Therefore, the potential benefits to the public, of having the claimed expressed polypeptides and the recited expressed polynucleotides, in terms of lives saved and reduced health care costs, are enormous. Evidence of the benefits of this information include the following

- In 1999, CV Therapeutics, an Incyte collaborator, was able to use Incyte gene expression technology, information about the structure of a known transporter gene, and chromosomal mapping location, to identify the key gene associated with Tangier disease. This discovery took place over a matter of only a few weeks, due to the power of these new genomics technologies. The discovery received an award from the American Heart Association as one of the top 10 discoveries associated with heart disease research in 1999.

- In an April 9, 2000, article published by the Bloomberg news service, an Incyte customer stated that it had reduced the time associated with target discovery and validation from 36 months to 18 months, through use of Incyte's genomic information database. Other Incyte customers have privately reported similar experiences. The implications of this significant saving of time and expense for the number of drugs that may be developed and their cost are obvious.

- In a February 10, 2000, article in the *Wall Street Journal*, one Incyte customer stated that over 50 percent of the drug targets in its current pipeline were derived from the Incyte database. Other Incyte customers have privately reported similar experiences. By doubling the number of targets available to pharmaceutical researchers, Incyte genomic information has demonstrably accelerated the development of new drugs.

Because the Patent Examiner failed to address or consider the "well-established" utilities for the claimed invention in toxicology testing, drug development, and the diagnosis of disease, the Examiner's rejections should be withdrawn regardless of their merit.

C. Objective evidence corroborates the utilities of the claimed invention

There is in fact no restriction on the kinds of evidence a Patent Examiner may consider in determining whether a "real-world" utility exists. "Real-world" evidence, such as evidence showing actual use or commercial success of the invention, can demonstrate conclusive proof of utility. *Raytheon v. Roper*, 220 USPQ2d 592 (Fed. Cir. 1983); *Nestle v. Eugene*, 55 F.2d 854, 856, 12 USPQ 335 (6th Cir. 1932). Indeed, proof that the invention is made, used or sold by any person or entity other than the patentee is conclusive proof of utility. *United States Steel Corp.* v.

Phillips Petroleum Co., 865 F.2d 1247, 1252, 9 USPQ2d 1461 (Fed. Cir. 1989).

Over the past several years, a vibrant market has developed for databases containing all expressed genes (along with the polypeptide translations of those genes). (Note that the value in these databases is enhanced by their completeness, but each sequence in them is independently valuable.) The databases sold by Appellants' assignee, Incyte, include exactly the kinds of information made possible by the claimed invention, such as tissue and disease associations. Incyte sells its database containing the claimed sequence and millions of other sequences throughout the scientific community, including to pharmaceutical companies who use the information to develop new pharmaceuticals.

Both Incyte's customers and the scientific community have acknowledged that Incyte's databases have proven to be valuable in, for example, the identification and development of drug candidates. As Incyte adds information to its databases, including the information that can be generated only as a result of Incyte's discovery of the claimed polypeptide, the databases become even more powerful tools. Thus the claimed invention adds more than incremental benefit to the drug discovery and development process.

III. The Patent Examiner's Rejections Are Without Merit

Rather than responding to the evidence demonstrating utility, the Examiner attempts to dismiss it altogether by arguing that the disclosed and well-established utilities for the claimed polypeptide are not "specific, substantial, and credible" utilities. (Final Office Action at p. 2) The Examiner is incorrect both as a matter of law and as a matter of fact.

A. Membership in a Class of Useful Products Can Be Proof of Utility

Despite the uncontradicted evidence that the claimed polypeptides are expressed polypeptides (encoded by expressed polynucleotides), the Examiner refused to impute the utility of the members of the family of expressed polypeptides to the claimed polypeptides. In the Office Action, the Patent Examiner takes the position that, unless Appellants can identify a specific biological activity for the claimed polypeptides, utility cannot be imputed.

In order to demonstrate utility by membership in a class, the law requires only that the class not contain a substantial number of useless members. So long as the class does not contain

a substantial number of useless members, there is sufficient likelihood that the claimed invention will have utility, and a rejection under 35 U.S.C. § 101 is improper. That is true regardless of how the claimed invention ultimately is used and whether or not the members of the class possess one utility or many. *See Brenner* v. *Manson*, 383 U.S. 519, 532 (1966); *Application of Kirk*, 376 F.2d 936, 943 (CCPA 1967).

Membership in a "general" class is insufficient to demonstrate utility only if the class contains a sufficient number of useless members such that a person of ordinary skill in the art could not impute utility by a substantial likelihood. There would be, in that case, a substantial likelihood that the claimed invention is one of the useless members of the class. In the few cases in which class membership did not prove utility by substantial likelihood, the classes did in fact include predominately useless members. *E.g.*, *Brenner* (man-made steroids); *Kirk* (same); *Natta* (man-made polyethylene polymers).

The Examiner addresses the claimed polypeptides as if the general class in which it is included is not the family of expressed polypeptides, but rather all polypeptides, including the vast majority of useless theoretical molecules not occurring in nature, and thus not pre-selected by nature to be useful. While these "general classes" may contain a substantial number of useless members, the family of expressed polypeptides does not. The family of expressed polypeptides is sufficiently specific to rule out any reasonable possibility that the claimed polynucleotides would not also be useful like the other members of the family.

Because the Examiner has not presented any evidence that the family of expressed polypeptides has any, let alone a substantial number, of useless members, the Examiner must conclude that there is a "substantial likelihood" that the claimed polypeptides are useful.

B. The Precise Biological Role Or Function Of An Expressed Polypeptide Is Not Required To Demonstrate Utility

The Patent Examiner's primary rejection of the claimed invention is based on the ground that, without information as to the precise "biological role" of the claimed invention, the claimed invention's utility is not sufficiently specific. See Office Action, mailed February 25, 2003 at p. 3. According to the Examiner, it is not enough that a person of ordinary skill in the art could use and, in fact, would want to use the claimed invention either by itself or in a 2-D gel or western

blot to monitor the expression of genes for such applications as the evaluation of a drug's efficacy and toxicity. The Examiner would require, in addition, that the applicant provide a specific and substantial interpretation of the results generated in any given expression analysis.

It may be that specific and substantial interpretations and detailed information on biological function are necessary to satisfy the requirements for publication in some technical journals, but they are not necessary to satisfy the requirements for obtaining a United States patent. The relevant question is not, as the Examiner would have it, whether it is known how or why the invention works, *In re Cortwright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999), but rather whether the invention provides an "identifiable benefit" in presently available form. *Juicy Whip Inc.* v. *Orange Bang Inc.*, 185 F.3d 1364, 1366 (Fed. Cir. 1999). If the benefit exists, and there is a substantial likelihood the invention provides the benefit, it is useful. There can be no doubt, particularly in view of the Furness Declaration (at, *e.g.*, ¶¶ 9-13), that the present invention meets this test.

The threshold for determining whether an invention produces an identifiable benefit is low. *Juicy Whip*, 185 F.3d at 1366. Only those utilities that are so nebulous that a person of ordinary skill in the art would not know how to achieve an identifiable benefit and, at least according to the PTO guidelines, so-called "throwaway" utilities that are not directed to a person of ordinary skill in the art at all, do not meet the statutory requirement of utility. Utility Examination Guidelines, 66 Fed. Reg. 1092 (Jan. 5, 2001).

Knowledge of the biological function or role of a biological molecule has never been required to show real-world benefit. In its most recent explanation of its own utility guidelines, the PTO acknowledged as much (66 F.R. at 1095):

> [T]he utility of a claimed DNA does not necessarily depend on the function of the encoded gene product. A claimed DNA may have specific and substantial utility because, *e.g.*, it hybridizes near a disease-associated gene or it has gene-regulating activity.

By implicitly requiring knowledge of biological function for any claimed polypeptide, the Examiner has, contrary to law, elevated what is at most an evidentiary factor into an absolute requirement of utility. Rather than looking to the biological role or function of the claimed invention, the Examiner should have looked first to the benefits it is alleged to provide.

C. The uses of SEQ ID NO:6 in toxicology testing, drug discovery, and disease diagnosis are practical uses beyond mere study of the invention itself

The Examiner's rejection of the claims at issue as not a "substantial" use is tantamount to a rejection based on an allegation that the only use of the claimed invention is as a tool for further research. See Office Action, mailed February 25, 2003, at p. 4. Because the Examiner's rejection assumes a substantial overstatement of the law, and is incorrect in fact, it must be overturned.

There is no authority for the proposition that use as a tool for research is not a substantial utility. Indeed, the Patent Office itself has recognized that just because an invention is used in a research setting does not mean that it lacks utility (Section 2107.01 of the Manual of Patent Examining Procedure, 8th Edition, August 2001, under the heading I. Specific and Substantial Requirements, Research Tools):

> Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds). An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the specific invention is in fact "useful" in a patent sense. Instead, Office personnel must distinguish between inventions that have a specifically identified substantial utility and inventions whose asserted utility requires further research to identify or reasonably confirm.

The PTO's actual practice has been, at least until the present, consistent with that approach. It has routinely issued patents for inventions whose only use is to facilitate research, such as DNA ligases, acknowledged by the PTO's Training Materials to be useful.

The subset of research uses that are not "substantial" utilities is limited. It consists only of those uses in which the claimed invention is to be an **object** of further study, thus merely inviting further research on the invention itself. This follows from *Brenner*, in which the U.S. Supreme Court held that a process for making a compound does not confer a substantial benefit where the only known use of the compound was to be the object of further research to determine its use. *Id.* at 535. Similarly, in *Kirk*, the Court held that a compound would not confer substantial benefit on the public merely because it might be used to synthesize some other, unknown compound that would confer substantial benefit. *Kirk*, 376 F.2d at 940, 945. ("What

appellants are really saying to those in the art is take these steroids, experiment, and find what use they do have as medicines.") Nowhere do those cases state or imply, however, that a material cannot be patentable if it has some other, additional beneficial use in research.

Such beneficial uses beyond studying the claimed invention itself have been demonstrated, in particular those described in the Furness Declaration. The Furness Declaration demonstrates that the claimed invention is a tool, rather than an object, of research, and it demonstrates exactly how that tool is used. Without the claimed invention, it would be more difficult to generate information regarding the properties of tissues, cells, drug candidates and toxins apart from additional information about the polypeptide itself.

The claimed invention has numerous other uses as a research tool, each of which alone is a "substantial utility." These include the use of the protein in screening assays to identify specific ligands.

D. The Patent Examiner Failed to Demonstrate That a Person of Ordinary Skill in the Art Would Reasonably Doubt the Utility of the Claimed Invention

The Examiner's primary grounds for rejection of either the well established or specific asserted utilities for the claimed polypeptide is based on an allegation that the skilled artisan would doubt the "substantial likelihood" that the instant protein of SEQ ID NO:6 would be expressed in proportion to its encoding mRNA, SEQ ID NO1.

In this respect, the Office Action has set forth the novel theory that the central dogma of molecular biology (*i.e.*, DNA directs transcription of messenger RNA which in turn directs translation of protein) somehow does not apply to the discoveries of the present application. That is, the nucleotide sequence of SEQ ID NO:1 (which encodes the polypeptide of SEQ ID NO:6) was determined from a human cDNA library. That cDNA library in turn was made from messenger RNA isolated from human tissue. See the Specification, for example, at pages 18-20. Thus, the nucleotide sequences of the present invention are expressed sequences. The Office Action purports that the existence of an expressed mRNA does not insure that the protein encoded by the mRNA will be translated and, hence, the claimed subject matter lacks patentable utility.

Regulation of gene expression occurs at many levels, including transcription, splicing,

polyadenylation, mRNA stability, mRNA transport and compartmentalization, translation efficiency, protein modification and protein turnover. While steady state mRNA levels are not always directly proportional to the amount of protein produced in a cell, mRNA levels are **routinely** used as an indicator of protein expression. Countless scientific publication have been based on data relating to mRNA levels when the polypeptide encoded by the mRNA was unknown or difficult to detect. Moreover, mRNA levels are **usually** a good indicator of protein levels in a cell. The Office Action cites a few examples of protein regulation downstream of transcription; however, these examples represent comparatively unusual mechanisms of gene regulation. According to B. Lewin [(1997) Genes VI Oxford University Press, Inc. New York, NY] (of record in the Response to Office Action, filed November 6, 2002):

> Transcription of a gene in the active state is controlled at the stage of initiation, that is, by the interaction of RNA polymerase with its promoter. This is now becoming susceptible to study in the *in vitro* systems... ***For most genes, this is a major control point; probably it is the most common level of regulation.*** [page 847, emphasis added].
>
> But having acknowledged that control of gene expression can occur at multiple stages, and that production of RNA cannot inevitably be equated with production of protein, it is clear that ***the overwhelming majority of regulatory events occur at the initiation o transcription. Regulation of tissue-specific gene transcription lies at the heart of eukaryotic differentiation.*** [pages 847-848, emphasis added]

Thus the question is not whether there is the potential for post-transcriptional regulation of SEQ ID NO:1 expression but whether one skilled in the art would have a reasonable expectation that SEQ ID NO:1 expression correlates with the levels of SEQ ID NO:6 mRNA. Applicants need only prove a "substantial likelihood" of utility; certainty is not required. *Brenner v. Manson*, 383 U.S. 519, 532, 148 USPQ 689 (1966). In the case of the instant invention, one skilled in the art would be imprudent in assuming, *a priori*, that protein levels did not correspond to mRNA levels and that levels of SEQ ID NO:6 were controlled predominantly in a post-transcriptional manner, thereby dismissing the significance of mRNA levels.

As further evidence of applicants assertion, the authoritative text in the field of molecular biology (*The Molecular Biology of the Cell*) indicates that the *predominant* level of control of gene expression is at transcription. For example, in discussing the complicated process of gene expression, Alberts et al. state,

> There are many steps in the pathway leading from DNA to protein, and all of them can in principle be regulated. Thus a cell can control the proteins it makes by (1) controlling when and how often a given gene is transcribed (transcriptional control), (2) controlling how the primary RNA transcript is spliced or otherwise processed (RNA processing control), (3) selecting which completed mRNAs in the cell nucleus are exported to the cytoplasm (RNA transport control), (4) selecting which mRNAs in the cytoplasm are translated by ribosomes (translational control), (5) selectively destabilizing certain mRNA molecules in the cytoplasm (mRNA degradation control), or (6) selectively activating, inactivating or compartmentalizing specific protein molecules after they have been made (protein activity control).
>
> **For most genes transcriptional controls are paramount**...Although all of the steps involved in expressing a gene can in principle be regulated, for most genes the initiation of RNA transcription is the most important point of control." (emphasis added).
>
> (The Molecular Biology of the Cell, Alberts B. et al., editors, Garland Publishing, Inc., 1994, 3rd Edition, page 403; Reference No. 5).

Even in discussing posttranscriptional controls, Alberts et al. state that, "[a]lthough controls on the initiation of gene transcription are the predominant form of regulation for most genes, other controls can act later in the pathway from RNA to protein to modulate the amount of gene product that is made" (page 453; Reference 5). Indeed Alberts et al. goes on to describe several examples of genes exhibiting posttranscriptional control. However, the fact that there are examples of genes that are regulated by posttranscriptional controls, does not detract from the observation that the *preponderance* of genes are regulated at the level of transcription. This, therefore supports Appellants' assertion that mRNA levels are *usually* a good indicator of protein levels.

IV. By Requiring the Patent Applicant to Assert a Particular or Unique Utility, the Patent Examination Utility Guidelines and Training Materials Applied by the Patent Examiner Misstate the Law

There is an additional, independent reason to overturn the rejections: to the extent the rejections are based on Revised Interim Utility Examination Guidelines (64 FR 71427, December 21, 1999), the final Utility Examination Guidelines (66 FR 1092, January 5, 2001) and/or the Revised Interim Utility Guidelines Training Materials (USPTO Website www.uspto.gov, March 1, 2000), the Guidelines and Training Materials are themselves

inconsistent with the law.

The Training Materials, which direct the Examiners regarding how to apply the Utility Guidelines, address the issue of specificity with reference to two kinds of asserted utilities: "specific" utilities, which meet the statutory requirements, and "general" utilities, which do not. The Training Materials define a "specific utility" as follows:

> A [specific utility] is *specific* to the subject matter claimed. This contrasts to *general* utility that would be applicable to the broad class of invention. For example, a claim to a polynucleotide whose use is disclosed simply as "gene probe" or "chromosome marker" would not be considered to be specific in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

The Training Materials distinguish between "specific" and "general" utilities by assessing whether the asserted utility is sufficiently "particular," *i.e.*, unique (Training Materials at p.52) as compared to the "broad class of invention." (In this regard, the Training Materials appear to parallel the view set forth in Stephen G. Kunin, Written Description Guidelines and Utility Guidelines, 82 J.P.T.O.S. 77, 97 (Feb. 2000) ("With regard to the issue of specific utility the question to ask is whether or not a utility set forth in the specification is *particular* to the claimed invention.").)

Such "unique" or "particular" utilities never have been required by the law. To meet the utility requirement, the invention need only be "practically useful," *Natta*, 480 F.2d 1 at 1397, and confer a "specific benefit" on the public. *Brenner*, 383 U.S. at 534. Thus incredible "throwaway" utilities, such as trying to "patent a transgenic mouse by saying it makes great snake food," do not meet this standard. Karen Hall, Genomic Warfare, The American Lawyer 68 (June 2000) (quoting John Doll, Chief of the Biotech Section of USPTO).

This does not preclude, however, a general utility, contrary to the statement in the Training Materials where "specific utility" is defined (page 5). Practical real-world uses are not limited to uses that are unique to an invention. The law requires that the practical utility be "definite," not particular. *Montedison,* 664 F.2d at 375. Appellant is not aware of any court that has rejected an assertion of utility on the grounds that it is not "particular" or "unique" to the specific invention. Where courts have found utility to be too "general," it has been in those cases

in which the asserted utility in the patent disclosure was not a practical use that conferred a specific benefit. That is, a person of ordinary skill in the art would have been left to guess as to how to benefit at all from the invention. In *Kirk*, for example, the CCPA held the assertion that a man-made steroid had "useful biological activity" was insufficient where there was no information in the specification as to how that biological activity could be practically used. *Kirk*, 376 F.2d at 941.

The fact that an invention can have a particular use does not provide a basis for requiring a particular use. *See Brana*, *supra* (disclosure describing a claimed antitumor compound as being homologous to an antitumor compound having activity against a "particular" type of cancer was determined to satisfy the specificity requirement). "Particularity" is not and never has been the *sine qua non* of utility; it is, at most, one of many factors to be considered.

As described *supra*, broad classes of inventions can satisfy the utility requirement so long as a person of ordinary skill in the art would understand how to achieve a practical benefit from knowledge of the class. Only classes that encompass a significant portion of nonuseful members would fail to meet the utility requirement. Montedison, 664 F.2d at 374-75.

The Training Materials fail to distinguish between broad classes that convey information of practical utility and those that do not, lumping all of them into the latter, unpatentable category of "general" utilities. As a result, the Training Materials paint with too broad a brush. Rigorously applied, they would render unpatentable whole categories of inventions heretofore considered to be patentable, and that have indisputably benefitted the public, including the claimed invention. Thus the Training Materials cannot be applied consistently with the law.

V. To the extent the rejection of the claimed invention under 35 U.S.C. § 112, first paragraph, is based on the improper rejection for lack of utility under 35 U.S.C. § 101, it must be reversed.

The rejection set forth in the Office Action is based on the assertions discussed above, i.e., that the claimed invention lacks patentable utility. To the extent that the rejection under § 112, first paragraph, is based on the improper allegation of lack of patentable utility under § 101, it fails for the same reasons.

(9) CONCLUSION

Appellants respectfully submit that rejections for lack of utility based, *inter alia*, on an allegation of "lack of specificity," as set forth in the Office Action and as justified in the Revised Interim and final Utility Guidelines and Training Materials, are not supported in the law. Neither are they scientifically correct, nor supported by any evidence or sound scientific reasoning. These rejections are alleged to be founded on facts in court cases such as *Brenner* and *Kirk*, yet those facts are clearly distinguishable from the facts of the instant application, and indeed most if not all nucleotide and protein sequence applications. Nevertheless, the PTO is attempting to mold the facts and holdings of these prior cases, "like a nose of wax,"[2] to target rejections of claims to polypeptide and polynucleotide sequences, as well as to claims to methods of detecting said polynucleotide sequences, where biological activity information has not been proven by laboratory experimentation, and they have done so by ignoring perfectly acceptable utilities fully disclosed in the specifications as well as well-established utilities known to those of skill in the art. As is disclosed in the specification, and even more clearly, as one of ordinary skill in the art would understand, the claimed invention has well-established, specific, substantial and credible utilities. The rejections are, therefore, improper and should be reversed.

Moreover, to the extent the above rejections were based on the Revised Interim and final Examination Guidelines and Training Materials, those portions of the Guidelines and Training Materials that form the basis for the rejections should be determined to be inconsistent with the law.

Claims 15, 16 and 19 stand further rejected under 35 U.S.C. 112, First Paragraph, based on an allegation that an immunogenic fragment of SEQ ID NO:6 or a pharmaceutical composition comprising the polypeptide of SEQ ID NO:6, or an immunogenic fragment of SEQ ID NO:6, are sufficiently described in the specification that one skilled in the art would recognize applicants possession of them in accordance with 35 U.S.C. §112, first paragraph.
The rejection alleges, in particular, that:

- Applicant is not in possession of the claimed proteins and immunogenic fragments

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[2] "The concept of patentable subject matter under §101 is not 'like a nose of wax which may be turned and twisted in any direction * * *.' *White v. Dunbar*, 119 U.S. 47, 51." *(Parker v. Flook,* 198 USPQ 193 (US SupCt 1978))

thereof, because one of skill in the art would reasonably conclude that the disclosure insufficiently provides written description regarding the biological activities or role(s) of the claimed protein.

- Also, "an immunogenic fragment" encompasses numerous polypeptide variants of the claimed protein (SEQ ID NO:6). One skilled in thea rt would reasonably conclude that the disclosure fails to provide a representative number of variants to describe the immunogenic fragments. Thus, applicant was not in possession of the pharmaceutical composition comprising the claimed protein and the claimed immunogenic fragment. Final Office, at page 4.

The claimed polypeptide, SEQ ID NO:6, immunogenic fragments thereof, and compositions thereof are sufficiently described for the skilled artisan to recognize applicants possession of them

The use of the polypeptide of SEQ ID NO:6, and consequently of immunogenic fragments of the polypeptide in preparing antibodies specific for SEQ ID NO:6, are sufficiently described for the reasons given in response to the rejection of claims under 35 U.S.C. § 101, that one would clearly know how to use them without undue experimentation.

With respect to an adequate description of immunogenic fragments of SEQ ID NO:6, applicants point out that methods of identifying suitable immunogenic fragments for any particular protein, including SEQ ID NO:6, are found in the specification, for example, in Example VIII at pp. 22-23 of the specification, as well as methods of making said antibodies (see specification, in particular, at p. 17, lines 18-31), and the fact that these methods are well known in the art (as well as well referenced in the specification). "A patent need not teach, and preferably omits what is well known in the art". See MPEP § 2164.01. It is well known in the art, and specifically stated in the specification, that suitable antigenic fragments for antibody production are at least 15 amino acid residues in length, and further addresses how to select appropriate such fragments from accessible regions of the molecule. See, in particular, the paragraph beginning at p. 22, line 34. Thus, the Examiner's contention that applicants claim to immunogenic fragments of SEQ ID NO:6 encompasses a large quantity (estimated by the Examiner to be at least 1.7×10^5) is unfounded. The Examiner discusses, at length, the issue of

how protein folding affects secondary structure and the uncertainty in identifying suitable antigenic epitopes in the folded structure of a protein. However, these considerations are also well known in the art, as well as disclosed in the specification. The specification describes, for example, the use of software such as LASERGENE (DNASTAR) for identifying regions of high immunogenicity based on hydrophobicity/hydrophilicity profiles that specifically locates the most likely exposed surface regions of the molecule thus substantially reducing the uncertainty in identifying suitable epitopes (see specification, at p 22 bridging p. 23).

Based on the disclosure of the specification and the level of one skilled in the art at the time the application was filed, it would therefore not require undue experimentation by the skilled artisan to identify and prepare suitable immunogenic fragments of SEQ ID NO:6 for antibody production, and to produce said antibodies.

With respect to claim 19, applicants point out that the claim does not recite a "pharmaceutical composition" as the Examiner alleges, rather a composition comprising a protein of claim 15 and a "pharmaceutical carrier". The use of such a composition for any number of reasons, such as for the stable storage of the isolated biological material, is readily apparent to the skilled artisan.

For all of the above reasons, applicants submit that the claimed polypeptides and compositions recited in claims 15, 16 and 19 are sufficiently described in the specification that the skilled artisan would recognize applicants possession of them at the time the application was filed and therefore request withdrawal of the rejection of these claims under 35 U.S.C. § 112, first paragraph.

Due to the urgency of this matter and its economic and public health implications, an expedited review of this appeal is earnestly solicited.

If the USPTO determines that any additional fees are due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108.**

This brief is enclosed in triplicate.

Respectfully submitted,

INCYTE CORPORATION

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Enclosures:

1. the Declaration of John C. Rockett, Ph.D., under 37 C.F.R. § 1.132, with Exhibits A-Q (hereinafter the "Rockett Declaration");
2. the Declaration of Tod Bedilion, Ph.D., under 37 C.F.R. § 1.132 (hereinafter the "Bedilion Declaration");
3. the Declaration of Vishwanath R. Iyer, Ph.D., under 37 C.F.R. § 1.132 with Exhibits A-E (hereinafter the "Iyer Declaration"); and
4. seven (7) references published before or shortly after the April 8, 1997 priority date of the instant divisional application:
   a) PCT application WO 95/21944, SmithKline Beecham Corporation, Differentially expressed genes in healthy and diseased subjects (August 17, 1995)
   b) PCT application WO 95/20681, Incyte Pharmaceuticals, Inc., Comparative gene transcript analysis (August 3, 1995)

c) M. Schena et al., Quantitative monitoring of gene expression patterns with a complementary DNA microarray, Science 270:467-470 (October 20, 1995)

d) PCT application WO 95/35505, Stanford University, Method and apparatus for fabricating microarrays of biological samples (December 28, 1995)

e) U.S. Pat. No. 5,569,588, M. Ashby et al., Methods for drug screening (October 29, 1996)

f) R. A. Heller al., Discovery and analysis of inflammatory disease-related genes using cDNA microarrays, Proc. Natl. Acad. Sci. USA 94:2150 - 2155 (March 1997)

g) PCT application WO 97/13877, Lynx Therapeutics, Inc., Measurement of gene expression profiles in toxicity determinations (April 17, 1997)

5. The Molecular Biology of the Cell, Alberts B. et al., editors, Garland Publishing, Inc., 1994, 3rd Edition, pages 403 and 453.

APPENDIX - CLAIMS ON APPEAL

15. (Previously Amended) A substantially purified protein expressed in response to polycyclic aromatic hydrocarbon exposure, comprising:

(a) a protein having an amino acid sequence of SEQ ID NO:6; and

(b) an immunogenic fragment of the protein of (a).

16. (Original) A protein of claim 15, comprising the amino acid sequence of SEQ ID NO:6.

19. (Original) A composition comprising a protein of claim 15 and a pharmaceutical carrier.